

## NUTRITIONAL AND HEALTH BENEFITS OF CURCUMIN

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*Review paper*

### Summary

Turmeric (*Curcuma longa*) belongs to the family *Zingiberaceae* and it has been traditionally used for centuries in Asian cuisine. India is the largest producer, consumer and exporter of turmeric. Its dried and ground tuber is used worldwide as a spice (the most famous spice which contains turmeric is *curry*) and as an additive for a variety of products that require medically acceptable intense yellow color. The most important part of the turmeric tuber is a group of bioflavonoids, i.e. curcuminoids (curcumin (77%), bisdemethoxycurcumin and demethoxycurcumin). The most common method for the isolation of curcumin is extraction with organic solvents, usually ethanol, by using Soxhlet, ultrasonic and microwave extraction, and more recently, due to increased use in the food industry (food supplements), triacylglycerol. Curcumin has significant anti-inflammatory, antioxidant, chemoprotective, anticancer, and gastroprotective properties. It affects the neurosystem and it is one of the most investigated bioflavonoids. The aim of this paper is to present the dietary and health benefits of turmeric and curcumin for both humans and animals.

**Keywords:** turmeric, spice, food and health benefits

### Introduction

Turmeric (*Curcuma*) - *Curcuma longa* L. (*Zingiberaceae*) is a perennial plant native to Southeast Asia; it has been used since ancient times as a spice, in medicine, and for coloring and flavoring food. In addition to *Curcuma longa* L., the genus turmeric contains about 30 other species. The name *Curcuma* is derived from the Arabic word "turmeric" which means yellow. In Sanskrit, turmeric has 55 different names associated with its religious and medical use (Ravindran, 2007). The varieties *Allepey* and *Madras* are mostly cultivated in India (82%), and its yield was around 720,000 tons in 2015/2016. The part of turmeric used in food and medicine is the rhizome. The rhizome is harvested, cleaned, and boiled until it becomes soft, and then dried in the sun in a 5-7 cm thick layer for about 2 weeks. The yield is 10-30%, depending on the variety and the cultivation area (Kandiannan et al., 2008). Dried product is milled and marketed. Products prepared in this way are used in diets as spices, and as the basic raw material for the production of the bioflavonoid curcumin. Curcumin is used as an additive (E100), and its main purpose is coloring products yellow and up to red, depending on the pH of the product. Curcumin is one of the most researched bioflavonoids today and a

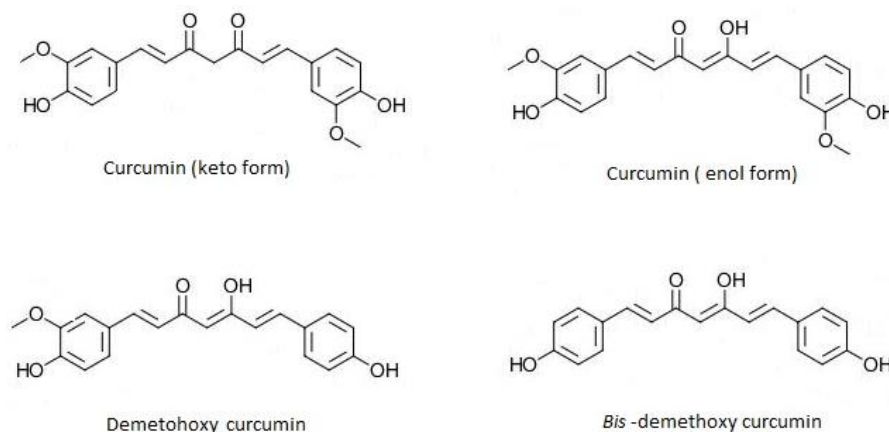
number of studies have confirmed its antioxidant, anti-inflammatory, anti-cancer, chemoprotective, gastroprotective, and many other health properties. Studies have shown that it is not toxic, even at doses up to 12 g / day, and it is tolerated very well by the human body (Basnet et al., 2011). Most studies have shown that the biological effect of curcumin in large part comes from its ability to directly bind to different proteins (cyclooxygenase, lipoxygenase) or to modulate the intracellular redox state (Srivastava et al., 2011).

The shortfall of this bioflavonoid is its relatively poor absorption, and it is therefore necessary to conjugate it. Recent research studies considered its adoption in the form of nanoparticles.

### *Preparation of curcumin and its use as a food additive*

*Curcuma longa* L. contains about 2-9% of curcuminoids. The most important of those are curcumin (77%), dimethoxy-curcumin (17%), and bis-demethoxy-curcumin (3%). These three compounds differ in the substitution of methoxy groups in the aromatic ring (Fig. 1).

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**Fig. 1.** Composition of curcumin

Curcumin (E,E) -1,7-bis (4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione) is extracted from the tubers of a dried and milled turmeric by using a suitable solvent. The oily resin is obtained after the extraction and removal of the solvent, and contains 25-35% of the pigment, along with the volatile oils and resin extracts. After the purification of the resin, approximately 90% of the pigment is obtained. The solvents which can be used for the extraction are: isopropanol, ethyl acetate, acetone, and ethanol. Curcumin is soluble in oils, insoluble in water at acidic and neutral pH, but soluble in alkaline conditions. The color of curcumin highly depends on the pH, at pH 2.5 to 7.0, it has an intense yellow color, and above pH 7.0 it is red.

For nutritional purposes, it is primarily used as an additive for coloring products. It is used in all sectors of the food industry, in the amount of 5-500 mg / kg, depending on the food category.

As an additive, curcumin is stable during thermal treatment and in dry food. It is relatively inert to reactions with other ingredients (may form salts with phthalates and citrates), and it is inert in the reactions with phosphates, chlorides, and bicarbonates (Stankovic, 2004).

Besides being used for food coloring, curcumin shows significant antioxidant properties and it prevents lipid peroxidation to a significant extent. The antioxidant properties are the result of the double carboxyl groups along with hydroxyl groups (Stankovic, 2004). Curcumin binds free radicals, and it becomes a short-lived, non-reactive free radical, and as such does not represent a health hazard (Majeed et al., 2000).

#### *The absorption and metabolic pathway of curcumin*

A number of previous studies have shown that curcumins exhibit poor bioavailability in the human body when

administered orally. It is due to their rapid degradation and poor absorption in the gastrointestinal tract, which results in low plasma concentrations and a very low distribution in tissues.

Curcumin in the body is converted into dihydrocurcumin (DHC), tetrahydrocurcumin (THC), hexahydrocurcumin (HHC), and octahydrocurcumin with reductase activity, and those are further decomposed by the action of  $\beta$ -glucuronidase to dihydrocurcumin-glucuronide and tetrahydrocurcumin -glucuronide (Pan et al., 1999). Poor absorption can be seen in the example of a clinical trial in which the oral intake of 3.6 g of standardized extract per day showed that one hour after intake the plasma concentration was only 11.1 mmol / L (Sharma et al., 2004). Due to this limitation, different formulations of curcumin were tested in order to maximize its availability and activity. In addition to oral intake, subcutaneous entry was investigated and has proven effective in keeping curcumin in tissues for a longer period (Shahani et al., 2010). Intravenous intake in the form of nanoparticles has been proven effective for the treatment of tumors in animals. (Kim et al., 2011) and Wang et al., 2008, Shi et al., 2011, showed that curcumin in liposomal form is effective in enhancing the effect of chemotherapy. The use of curcumin on the skin has proven to be very effective in treating certain types of psoriasis, wound healing, candidiasis, etc. (Prasad et al., 2014). Recent research has shown that oral intake in the form of nanoparticles increases the availability of curcumin 5-6 times in comparison to the standardized extract, due to increased water solubility it dissolves better in the digestive system and its degradation is longer (Xie et al., 2011). Nanoparticles are also safe, non-toxic, biodegradable, do not cause allergies in the body, and can be designed to be time releasing (Sankar et al., 2016). The combination of curcumin with piperine, liposomal, and phospholipid complexes also increases

bioavailability (Prasad et al., 2014). A hydrophilic carrier dispersed curcuminoid formula exhibits 46 times the bioavailability of the standard purified 95 percent curcuminoid preparation (Douglass and Clauatre, 2015).

#### *Antioxidant properties of curcumin*

Curcumin shows very significant antioxidant properties as a food additive. In the presence of curcumin, the oxidation of linoleic acid is very slow, and the antioxidant effect is about 80% (Jayaprakasha et al., 2006) when used as a dietary supplement. It works in a way that binds free radicals and it also donates a hydrogen atom (responsible for its antioxidant properties) (Wei et al., 2006). Curcumin has a property of donating electrons in order to neutralize free radicals by creating stable products, and thus breaking a chain reaction of creating free radicals in a living organism. Curcumin's ability of capturing hydrogen peroxide is higher than that of the commercial antioxidants (BHA, BHT, vitamin E) at the same concentration (20 mM) (Ak and Gülcin, 2008).

Curcumin shows a significant effect on hepatic oxidative stress in diets with high cholesterol by reducing antioxidative liver enzymes (catalase, glutathione peroxidase, and superoxide dismutase), it also reduces TNF- $\alpha$  (tumor necrosis factor alpha), serum IL-6 (interleukin 6), liver enzymes, and heart disease enzyme markers. Supplementation of curcumin in patients with hyperlipidemia can reduce cardiovascular problems (Hussein et al., 2016).

The study on oxidative stress and the loss of vitamins C and E during sleep in an area with little or no gravity (astronauts) showed that curcumin reduces the loss of these vitamins (Rai et al., 2010).

Curcumin prevents oxidation and lipid modification of low density lipoproteins, and as a consequence, the inhibition of prostacyclin (PGI<sub>2</sub>), which contributes to the formation of thrombosis and arteriosclerosis, and thus contributes to the prevention of the same (Mahfouz et al., 2009).

#### *Anti-inflammatory activity*

Curcumin reduces the response of specific proteins - cytokines that occur in the processes of inflammation, such as TNF- $\alpha$ , interleukins (IL-1, IL-2, IL-6, IL-8, IL-12), chemokines, through the inhibitory effect on NF- $\kappa$ B (cellular factor kappa B), and even directly binding to TNF- $\alpha$  (Anthwal et al., 2014). A series of studies on animals have shown that the dose of 100-200 mg per kg of body weight indicates good anti-inflammatory activity (Kohli et al., 2004). Curcumin reduces the inflammation associated with colitis by significantly reducing the activity of myeloperoxidase and TNF- $\alpha$  (Basnet et al.,

2011). Liu et al. (2015) have shown that curcumin reduces the pathological changes in the lungs and the accumulation of inflammatory cells in the airways of asthmatic mice by downregulating the expression of pro-inflammatory cytokines with the activation of the Nrf2 / HO-1 (nuclear factor erythroid 2-related factor / heme oxygenase-1) signaling pathway. Nuclear factor erythroid 2-related factor (Nrf2) is a cytoprotective factor which regulates the expression of gene coding for antioxidant, anti-inflammatory, and detoxifying proteins.

Pancreatitis is another inflammatory process associated with the secretion of NF- $\kappa$ B cytokines. Curcumin significantly reduces the activation of this cytokine and AP-1 (activator protein 1), and reduces the mRNA induction of iNOS (nitric oxide synthase), TNF- $\alpha$  and IL-6 cytokines in the pancreas (Gulcubuk et al., 2013).

Studies on the effects of curcumin on allergies have shown that curcumin inhibits the NF- $\kappa$ B in the airway, together with the transcription factor GATA3, reduces IgE in serum, and inhibits the Notch1-GTA3 signaling pathway (Chong et al., 2014).

#### *Anticancer activity*

The transcription factor NF- $\kappa$ B has the main role in the creation of tumors and inflammation, and the goal of most pharmaceutical and entomological preparations is to reduce its hyper productivity. Curcumin is a natural product which reacts with various compounds in the downstream of the NF- $\kappa$ B pathway. Curcumin blocks IKK activation, phosphorylation, and the degradation of I $\kappa$ B $\alpha$  (Kastori et al., 2015, Fiala, 2015). A large number of curcumin analogues were investigated in order to improve its efficiency in blocking NF- $\kappa$ B, including the latest analogs called BAT (Katsori et al., 2011, Kasinski et al. 2008). Katsori et al. (2015) have shown that the curcumin analog BAT3 selectively inhibits NF- $\kappa$ B dependent gene expression by binding to chromatin DNA in the laboratory. Curcumin inhibits the growth of androgen-independent prostate cancer cells through ERK1/2- and SAPK/JNK-mediated inhibition of p65, followed by the reducing expression of MUC1-C protein. The MUC1-C is a protein that has a markedly increased expression in prostate tumors (Li et al., 2015). In combination with  $\alpha$ -tomation, It is also effective in inhibiting PC3 prostate tumor cells by inhibiting the NF- $\kappa$ B and decreasing the expression of the Bcl-2 gene (Huang et al., 2015). Khosropanah et al. (2016) formulated curcumin nanoparticles to increase its bioavailability and to study the effect on breast cancer cells (MDA-MB 231), i.e. cytotoxicity on tumor cells. More than 50% of the tumor cells died within 48 hours after the administration of curcumin. The dosage of nano-formulated curcumin in this study was effective in half the dosage of the regular preparation of curcumin.

There search on gastrointestinal tract tumors has shown that curcumin in combination with quercetin (enhances the absorption of curcumin) inhibits phosphorylase AKT and ERK and induces apoptosis through a mitochondrial pathway (Zhang et al., 2015). Sridhar et al. (2014) researched the effect of the nanoparticles on a breast tumor culture (MCF7) and a lungs culture (A459), and in both cases the nanoparticles composed of 1% aloe vera gel and 5% curcumin showed 15% higher cytotoxicity than nanoparticles with conventional antitumor drugs. Some of the most important anticancer activities of curcumin are summarized in Table 1.

**Table 1.** The anticancer activities of curcumin (Bar-Sela et al., 2010)

Immunologic modulation
Radiosensitization and radioprotection
Chemopreventive, chemotherapeutic
Inhibition of angiogenesis and metastasis
Chemosensitizing activity
Inhibition of NF- $\kappa$ B
Downstream of NF- $\kappa$ B: Inhibition of cyclin D1
Downstream of NF- $\kappa$ B: Inhibition of COX-2
Downstream of NF- $\kappa$ B: Suppression of Bcl-2 and Bcl-XL
Inhibition of cytokines inhibits the pro-survival kinase Akt
Induction of phase II enzymes
Modulation of growth factors and their signaling pathway
Inhibition of STAT3 activation

#### *Antimutagenic, antimicrobial and gastroprotective effect*

Heterocyclic amines are formed during the processing of protein rich food at high temperatures and are known for their carcinogenic effect. The study was conducted in order to explain the antimutagenic properties of curcumin, and it showed that all three curcumins are very effective in preventing S9 mediated mutagenicity (> 80%) at a concentration of 200  $\mu$ g. Unsaturation in the side chain, a methoxy group on the benzene ring, and a central b-diketone moiety in the curcumin molecule are responsible for its high antimutagenic potential (Shishu and Kaur, 2008).

Curcumin shows significant antimicrobial properties. Studies carried out on G + (*B. cereus* and *S. aureus*) and G - (*E. coli* and *Y. enterocolitica*) bacteria have shown that curcumin and curcumin  $\beta$  glycoside at the concentration of 0.2-0.7  $\mu$ M, have a 100% inhibitory effect on the tested G + bacteria and *Y. enterocolitica*, while they have a slightly lower effect on the *E. coli* (70%) (Parvathy et al., 2009). Wang et al. (2016) examined the effect of curcumin on the development of pneumonia in mice caused by *Staphylococcus aureus* and showed that curcumin

effectively blocks the development of pneumonia by binding to  $\alpha$ -hemolysin (virulence factor and toxin secreted by *S. aureus*).

Curcumin is highly effective in suppressing *Helicobacter pylori* in the stomach. Research has shown that curcumin inhibits the shikimate path required for the synthesis of the bacteria aromatic ring, and therefore its growth. The histological analysis in the same study showed that curcumin also restores damaged cell walls of the stomach caused by *Helicobacter pylori* (De et al., 2009).

## Conclusions

In the past 30 years, numerous studies of curcumin's effect on cell tissues and animals, as well as clinical studies, have shown its multiple medical benefits (more than 10,000 published papers in the last 10 years). Despite its very poor bioavailability and absorption in the body tissues, curcumin has been recognized as an important therapeutic natural product. The highest medical value of curcumin is its strong antioxidant effect and its binding to inflammatory transcription factors as to precursors whether chronic diseases or tumors. Despite the large number of papers, a very small number of clinical trials were conducted specifically on humans in order to fully confirm and prove its effectiveness.

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